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The Pharmacokinetic Profile of Tamsulosin Oral Controlled Absorption System (OCAS®)

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Abstract

Context: A new formulation of tamsulosin for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) has been developed. This formulation uses the proprietary oral controlled absorption system (OCAS®) technology which has the potential to better control the release during passage of the gastrointestinal tract including the colon and which may be devoid of a food effect. This study describes the characteristics of the tamsulosin OCAS formulation with respect to single and multiple dose human pharmacokinetics (PK).

Methods: The single dose PK of three tamsulosin OCAS 0.4 mg formulations (S2, S3 and S4) in comparison with tamsulosin modified release (MR) 0.4 mg capsules were analysed in 12 young healthy volunteers in a 4-way crossover study to allow selection of a candidate for further development.

24 young healthy volunteers were subsequently recruited to compare multiple dose PK for tamsulosin OCAS 0.4, 0.8 and 1.2 mg S3 formulation under fasted conditions with tamsulosin OCAS 0.4 mg under fed conditions in a 4-way crossover study.

Results: The tamsulosin OCAS S3 formulation was selected for further development. This chosen formulation shows distinctively different PK from the commercially available tamsulosin MR capsules with a lower maximum plasma concentration (C_{max}), a slightly lower area under the curve (AUC) and reduced fluctuation in 24-hour plasma concentrations/improved C_{max}/C_{24h} ratio while showing dose linearity and an unchanged elimination half-life. It will allow once daily dosing in the treatment of LUTS/BPH. In addition, tamsulosin OCAS does not have a food effect unlike the MR capsules.

Conclusions: Tamsulosin OCAS shows improved PK compared with the standard MR capsules. Such improved PK may translate in an improvement of the efficacy/safety ratio during the treatment of LUTS/BPH. Demonstration of such potential benefits as well as the establishment of the daily dose will require subsequent confirmatory clinical studies.

Keywords: Tamsulosin; Controlled release formulation; Oral controlled absorption system; Benign prostatic hyperplasia; Lower urinary tract symptoms; Pharmacokinetics; Food effect

1. Introduction

Tamsulosin is an α_1-adrenoceptor (AR) antagonist that has been developed for the treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). Since its introduction in the 1990's, it has evolved into the most commonly used α_1-AR antagonist in this indication [1] due to its favourable efficacy/safety ratio [2–8] which is explained by the combination of its relative selectivity for the α_{1A}- and α_{1D}-AR subtypes, the selective distribution to prostatic tissue and its modified release (MR) formulation [8–11].

Nevertheless, the available tamsulosin MR capsule formulation has been associated with some drawbacks. For example, absorption of tamsulosin from the MR 0.4 mg capsules is food dependent. If it is taken in the

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fasting state, maximum plasma concentration (C_{max}) and the area under the curve (AUC) increase by about 70% and 30%, respectively, compared to when it is taken after breakfast [12]. Therefore, the labelling information recommends that tamsulosin MR should be dosed after breakfast or the first meal of the day. Lack of compliance with this dosing recommendation will therefore cause increased exposure to tamsulosin, which can lead to a higher risk for vasodilatation-related adverse events (AE) like dizziness, headache, asthenia, tachycardia/palpitation, orthostatic hypotension and syncope [13]. In addition, further smoothening of the plasma concentration time curve and providing more constant 24-hour plasma concentrations may lead to continued improvement of the efficacy/tolerability or risk/benefit ratio of tamsulosin.

2. Modified release formulations in the treatment of LUTS/BPH

The development of new pharmaceutical formulations is a long recognised way of improving the convenience and/or risk/benefit ratio of well established medicinal products [14]. In particular the development of once daily formulations of drugs that have to be dosed several times a day can lead to an improvement of compliance with pharmacotherapy. Improved safety and/or efficacy can especially be achieved by better controlling the release and absorption of drugs in the gastrointestinal (GI) tract and specifically in the colon, which will enable once daily administration resulting in a continuous 24-hour pharmacological effect [15].

In the area of LUTS/BPH, several MR formulations are available. These include the already mentioned MR capsule formulation of tamsulosin, the prolonged release (XL) formulation of alfuzosin [16–18] and the gastro-intestinal therapeutic system (GITS) formulation for doxazosin [19,20]. Fig. 1 illustrates the different technologies used for these products. The tamsulosin MR capsule utilises the well-established multi-unit layer coated pellet technology. The pellets have a drug core and the MR characteristics are provided by the layer surrounding the pellets. In the GI tract the pellets are hydrated and the drug is released. Doxazosin GITS uses the osmotic pump technology (OROS®) developed by Alza: the influx of water through the semi-permeable membrane of the tablet causes the polymeric push compartment to swell and the drug is pushed from the reservoir through small orifices in the tablet mantle into the GI tract. This provides a slow, sustained and controlled release rate for over 24 hours. Alfuzosin XL uses the Geomatrix® technology developed by Skye Pharma. An inactive swellable and an inactive erodable planar barrier layer bracket the hydrophilic layer of the tablet that contains the active ingredient. In the presence of water the hydrophilic layer expands and provides controlled drug release for more than 20 hours.

All technologies described above are dependent on the presence of water in the GI tract to release the active ingredient. Consequently drug release (and hence absorption) is impeded during the passage of the formulation through the colon where the amount of water is very limited. To make a new formulation of tamsulosin which would further smoothen the plasma

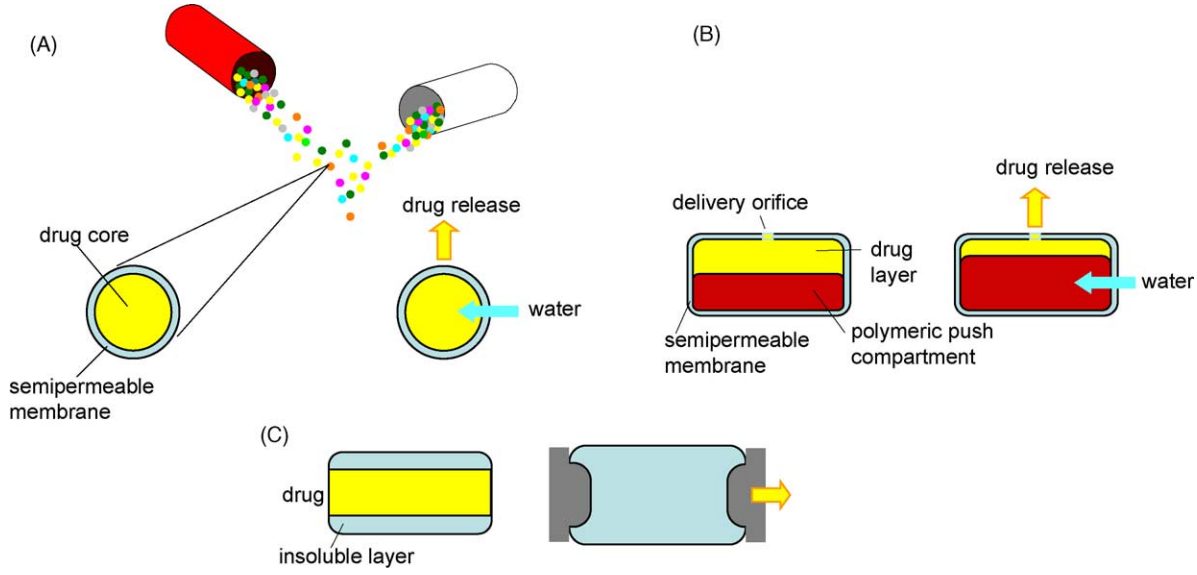

Fig. 1. Schematic representations of different MR technologies: (A) multi-unit membrane-coated pellets, (B) Oros®, (C) GeoMatrix®.

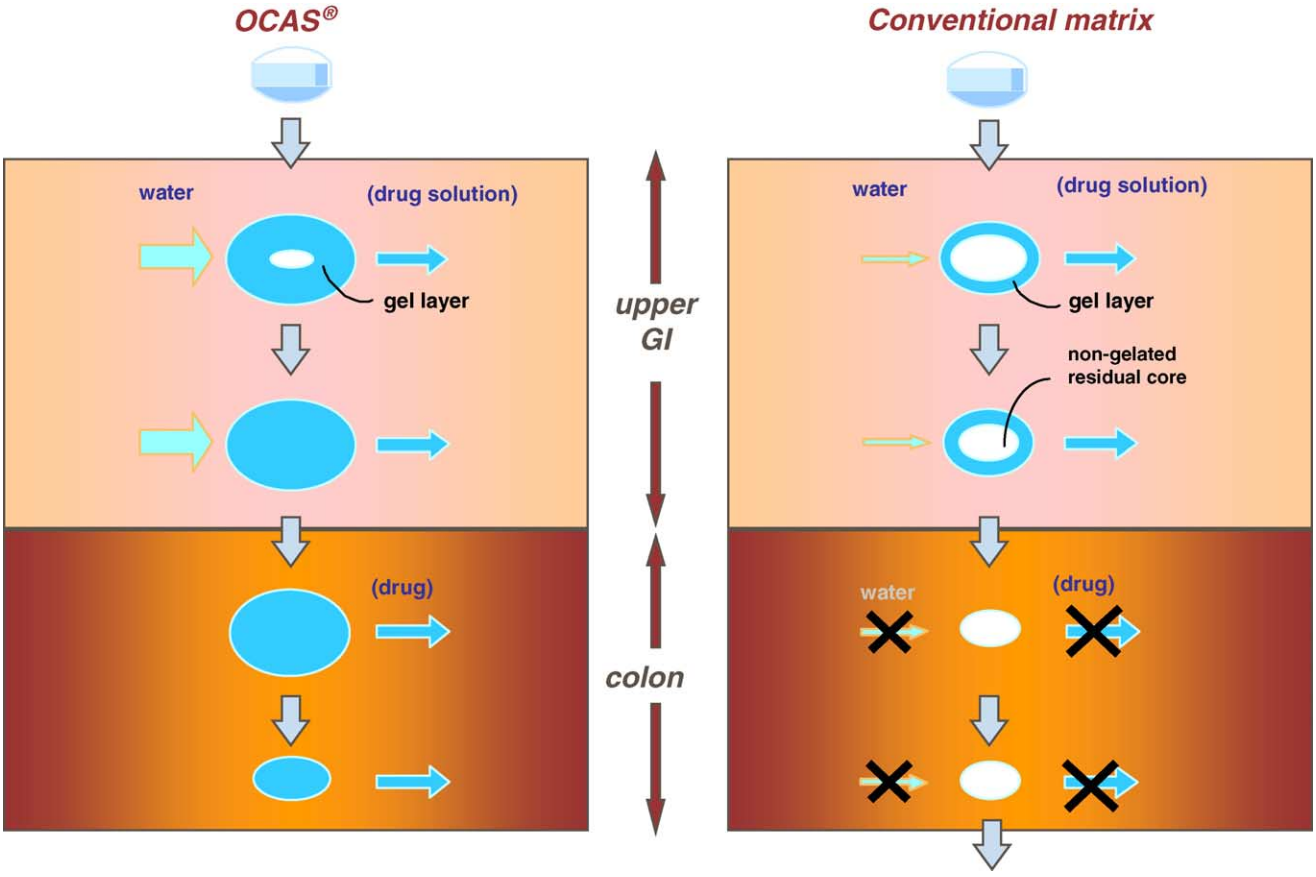

Fig. 2. Schematic representation of OCAS® hydration and drug release in small intestine and colon compared with conventional matrix hydration.

concentration over time profile and to obtain more constant 24-hour plasma concentrations of tamsulosin without a food effect, a novel oral controlled absorption system (OCAS®) was used to overcome the low absorption from the colon. The OCAS® formulation is a controlled release system of a gel matrix type that is composed of a gel-forming agent and a gel-enhancing agent as its major components. This OCAS® technology has been shown to provide pH-independent drug release and GI-agitation resistant gel formation [21]. The design concept is to achieve constant drug release, throughout the GI tract including the colon. The concept is illustrated in Fig. 2. The specific feature of this controlled release system is a very rapid hydration of the gel matrix such that complete hydration occurs prior to arrival of the dosage form at the colon; then the gel matrix has sufficient gel strength and can achieve drug release in the colon where water is poorly available [21]. This concept of limited drug release in the upper GI area and continued drug release in the lower GI area with the OCAS® technology should result in a more constant exposure to tamsulosin over 24 hours with a smaller peak-to-trough fluctuation (PTF) than the MR capsules. It is also expected that the food effect will be eliminated or at least decreased. Tamsulosin OCAS® may provide a safe once daily treatment of LUTS/BPH, enabling a constant release of tamsulosin over a 24-hour period and which can be given without dose titration, without an effect on blood pressure, without food effect and without the risk for orthostatic hypotension.

This paper describes the PK of single dose and multiple dose studies with tamsulosin OCAS® tablets in comparison with tamsulosin MR capsules and assesses the food effect of this new formulation.

3. Materials and methods

3.1. Ethics

The single and multiple dose studies were conducted in accordance with the Declaration of Helsinki and the ICH Guidelines on Good Clinical Practice (CPMP/ICH/135/95, approved on 17 July 1996). The protocol was approved by the Research Ethics Committee of The Queen's University of Belfast, Grosvenor Road, Belfast, Northern Ireland. All subjects were screened within 14 days prior to entering the study. Prior to screening, a specific screening informed consent form was signed.

3.2. Preparation of tamsulosin OCAS tablets

Macrogol 7,000,000, which has suitable gel strength, was used as the gel-forming agent and macrogol 8000, which has high water solubility, as the gel-enhancing agent. These two ingredients were used in the ratio 5:1. The *in vitro* dissolution rate appeared to be inversely proportional to the mass of macrogol in the matrix, meaning that a higher content of macrogol results in a slower dissolution rate. Due to the non-ionic structure of the matrix the dissolution rate was not greatly affected by pH.

Three tamsulosin 0.4 mg tablet formulations with identical macrogol 7,000,000 to 8000 ratios (5:1) but varying total macrogol contents: S2 (180 mg per tablet), S3 (240 mg per tablet) and S4 (300 mg per tablet), and therefore with different dissolution profiles, were selected for testing in phase 1 studies. The results of dissolution testing of these three formulations are given in Fig. 3.

The preparation of the investigational medicinal product took place under European Union Good Manufacturing Practices.

3.3. Study design

The PK of tamsulosin OCAS were evaluated in two studies. In the first study, single dose PK of three different tamsulosin OCAS 0.4 mg formulations (S2, S3 and S4) under fasted conditions and tamsulosin 0.4 mg MR capsules under fed conditions were assessed in a 4-way randomised, crossover way to select a formulation for further development. Tamsulosin MR was administered according to labelling, i.e. after food. As food might have interfered with the selection of the most appropriate OCAS formulation, tamsulosin OCAS was administered under fasting conditions. Single dose assessment days were separated by a wash-out period of at least 7 days.

In the second study, multiple dose PK of 0.4, 0.8 and 1.2 mg tamsulosin OCAS of the selected (S3) formulation from study one in the fasted state and 0.4 mg tamsulosin OCAS of the same formulation in the fed state were subsequently assessed in a randomised 4-way crossover way. Steady state following multiple dosing was considered to be achieved after a dosing period of 5 days. Dosing periods between crossovers were separated by a wash-out period of at least 7 days.

3.4. Study population (inclusion/exclusion criteria)

Healthy male Caucasian volunteers, age 18 to 45 years (inclusive), body weight between 60 and 100 kg (inclusive) and a body mass index $\leq$30 kg/m^2 were selected for both studies. Subjects with any clinically significant history of any disease or disorder were excluded. Also subjects with any clinically significant history of upper GI symptoms (such as nausea, vomiting, abdominal discomfort or upset, or heartburn) in the four weeks prior to admission to the clinical unit and subjects with any major surgery of the GI tract including cholecystectomy, but not appendectomy, were excluded from the studies.

3.5. Treatment and study procedures

In the first study, subjects were brought into the unit at 5.00 PM on Day 0 and dosed on Day 1 with the investigational medicinal product (tamsulosin OCAS tablets or tamsulosin MR capsules) around 9.00 AM. Fasting was maintained until four hours after dosing. Tamsulosin MR 0.4 mg capsules were given after a low fat breakfast. The subjects were kept in the unit until the morning of Day 4 of every study period.

In the second study each study period took nine days. Subjects were admitted to the unit on the day before first dosing (Day 0) until the morning of Day 7 after which they were allowed to leave but had to come back for the last measurements on Day 8. Dosing took place on Days 1–5 of the study period and the PK profile was determined after the dosing on Day 5. Subjects assigned to a fasting group were given a light snack on the evening preceding the dosing for PK measurement and were then kept fasting until dosing 11 hours later. The subjects assigned to the fed group were given a low fat breakfast 10 minutes before dosing.

All dosing in both studies was done together with 200 ml water.

3.6. Pharmacokinetics

Blood sampling was done pre-dose and at 1, 2, 3, 4, 5, 6, 7, 9, 12, 16, 24, 36, 48, and 72 h after dosing on Day 1 of each study period (in study one) or pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 12, 48 and 72 h after dosing on Day 5 of each study period in study two. Blood samples were collected into standard polypropylene tubes containing lithium-heparin as anticoagulant and labelled appropriately. After collection, blood samples were kept chilled in ice until ready for centrifuging which was done within 30 minutes of collection. The samples were centrifuged at about 4 °C for 10 minutes at 1500 g (3500 rpm). All the plasma (approximately 3 ml from a 6 ml blood sample) was harvested and divided over two appropriately labelled polypropylene tubes. Each individual's samples were stored as a package for that individual at −20 °C. At the end of each study day the samples were transferred to a freezer operating at −70 °C.

In study one the tamsulosin concentration in the blood samples was determined by using a validated high performance liquid chromatography (HPLC) method with fluorescence detection and a lower limit of quantification of 0.5 ng/ml [22]. The bioanalytical method for the quantification of tamsulosin HCl in human plasma in study two was based on HPLC-mass spectrometry (HPLC-MS). After addition of AB-289 (internal standard) to 200 μl of plasma, tamsulosin and the internal standard were extracted from plasma using liquid-liquid extraction (ethylacetate: cyclo-hexane (3:1 %v/v)) under alkaline conditions. The organic phase was removed and evaporated at 50 °C and the residue was re-dissolved in 100 μl of 20 mM ammonium acetate: acetonitrile (9:1 %v/v). A volume of 25 μl was injected into an LC-MS/MS system to separate tamsulosin and the internal standard from matrix constituents using Waters Symmetry® C18 material with a mean size of 3.5 μm in a stainless steel column of 100 mm × 2.1 mm. Detection was performed using a triple stage quadrupole mass spectrometer (Thermo Finnigan Surveyor and Thermo Finnigan TSQ 7000). Tamsulosin parent/daughter ions were detected with M/z = 409.2/228.0; the internal standard AB-289 parent/daughter ions at M/z = 423.2/285.1. This method is suitable for the quantification of tamsulosin (as tamsulosin HCl) in human plasma at concentrations ranging between 0.10 and 50 ng/ml.

PK data analysis of tamsulosin was performed using the PK data management software package WinNonlin (Pharsight Corp., Mountain View, CA, USA). The following PK parameters for plasma were calculated: after single and multiple dose C_{max}, time to reach C_{max} (t_{max}) and terminal elimination half-life ($t_{1/2}$); AUC from t = 0 to infinity (AUC_{0-inf}) after single dose and AUC from t = 0 to t = 24 h (AUC_{0-24h}) after multiple dose.

3.7. Assessments of safety/tolerability

Safety laboratory tests (haematology, biochemistry and urinalysis) were done at the pre-study screening, on admission and discharge of each study period and at the post-study screening visit. Blood pressure, pulse rate and respiration rate (study one only) were assessed throughout the study periods.

Adverse events (AEs) were obtained by questioning the subjects at regular time intervals, without using leading questions. Furthermore subjects were asked to report any events experienced throughout the study. All AEs were subjected to a causality assessment and they were coded using the Coding System for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary.

3.8. Statistical methods and sample size

Data of the PK parameters were summarised using descriptive statistics. For the assessment of the food effect, data of AUC_{0-24h} and C_{max} (after logarithmic transformation) were subjected to Analysis of Variance (SAS PROC GLM) taking into account the design factors subject, period and treatment followed by calculation of the 90%-confidence limits for the ratios of tamsulosin OCAS S3 1.2, 0.8 mg fasting and 0.4 mg fed vs. tamsulosin OCAS S3 0.4 mg fasting. Untransformed data of $t_{1/2}$ were subjected to Analysis of Variance (SAS PROC GLM) including the same factors followed by calculation of the 90%-confidence limits for the difference between tamsulosin OCAS S3 1.2, 0.8 mg fasting and 0.4 mg fed and tamsulosin OCAS S3 0.4 mg fasting. The t_{max} data were analysed by the non-parametric Friedman's test.

4. Results

4.1. Number of subjects

37 subjects were screened to enrol 15 subjects for study one. The subjects were aged between 19 and 44 years (mean 29 years), had a body weight between 62 and 88 kg (mean 73 kg) and a body mass index between 19.6 and 28.4 kg/m^2 (mean 24.1 kg/m^2). Three subjects were withdrawn during study period one (two for personal reasons, one because of a dosing error) and were replaced by three new subjects. The safety data of the discontinued subjects were included in the safety analysis ($n = 15$). Twelve subjects completing all four periods were included in the PK analysis.

51 subjects were screened to enrol 24 subjects for study two. All 24 subjects enrolled completed the whole study. The age ranged from 19 to 44 years (mean 29 years), body weight was between 60 and 100 kg (mean 80 kg) and body mass index varied between 19.4 and 29.5 kg/m^2 (mean 24.6 kg/m^2).

Table 1
Single dose PK parameters of three different tamsulosin OCAS 0.4 mg formulations/tablets (fasted) and tamsulosin MR 0.4 mg capsules (fed)

	Tamsulosin MR ($n = 12$)	Tamsulosin OCAS S2 ($n = 12$)	Tamsulosin OCAS S3 ($n = 12$)	Tamsulosin OCAS S4 ($n = 12$)
AUC_{last} (ng·h/ml)	253.7	191.9	175.7	148.6
	(53.2%)	(49.7%)	(53.5%)	(59.1%)
	93–501	70–371	70–413	64–341
	238.0	183.2	155.4	126.8
AUC_{0-inf} (ng·h/ml)	277.0	216.5	201.6	177.2
	(53.4%)	(48.6%)	(51.6%)	(54.9%)
	105–559	81–409	95–470	80–385
	260.1	198.0	177.7	160.1
AUC extrapolated (%)	8.46	11.94	13.83	17.21
	(37.6%)	(40.9%)	(51.0%)	(49.0%)
	3.8–14.4	6.7–21.5	6.3–26.7	8.2–39.5
	8.47	10.33	11.84	13.75
t_{max} (h)	6.67	5.83	8.51	8.18
	(18.4%)	(25.2%)	(86.1%)	(91.1%)
	5.0–9.0	4.0–9.0	3.0–24.0	3.0–24.0
	6.00	5.51	5.99	5.02
C_{max} (ng/ml)	13.74	7.13	5.88	5.17
	(41.8%)	(38.5%)	(44.3%)	(39.5%)
	6.3–26.5	2.9–12.9	3.5–12.2	2.8–9.7
	12.35	6.29	5.13	4.57
$t_{1/2}$ (h)	16.13	18.56	18.67	18.37
	(30.4%)	(31.4%)	(37.4%)	(28.3%)
	8.0–24.8	9.3–29.6	9.9–33.7	13.1–29.3
	15.95	17.77	18.37	16.72
t_{lag} (h)	0.84	0.00	0.00	0.00
	(46.7%)	(0.0%)	(0.0%)	(0.0%)
	0.0–1.0	0.0–0.0	0.0–0.0	0.0–0.0
	1.02	0.00	0.00	0.00

Each cell contains the arithmetic mean, the coefficient of variation between brackets, the range and the median.

4.2. Single dose pharmacokinetics

The estimated PK parameters of study one in which single doses of tamsulosin MR 0.4 mg capsules (fed) were compared with three different tamsulosin OCAS 0.4 mg formulations (S2, S3 and S4) given in fasted condition are presented in Table 1. Tamsulosin MR 0.4 mg capsules under fed conditions showed the well established PK profile with a t_{max} around 6 h, a C_{max} around 14 ng/ml and a $t_{1/2}$ around 16 h. The PK profile of the OCAS 0.4 mg formulations was clearly different from the tamsulosin MR 0.4 mg capsules. Even though the first plasma peak was reached at about the same time as with tamsulosin MR capsules, the mean C_{max} concentrations were clearly lower. For tamsulosin MR capsules, plasma concentrations declined consistently after reaching C_{max} without the occurrence of a second peak. However, for the OCAS formulations S3 and S4 plasma concentrations started to increase again 16 h after administration. A second maximum/shoulder was reached 24 h after administration. Generally this second peak was lower than the first one, but for some subjects the second peak represented the actual maximum. For OCAS S2 a kind of plateau was attained 16 to 24 h after administration.

Using the mean C_{max} and C_{24h} ratio, there was a 2.9-fold difference between these values for the MR capsule, a 1.8-fold difference for OCAS S2, a 1.4-fold difference for OCAS S3 and a 1.5-fold difference for OCAS S4. This reduced fluctuation in plasma concentrations clearly illustrates the smoothened controlled release characteristics of the three tamsulosin OCAS formulations.

None of the tamsulosin OCAS formulations can be considered to be bio-equivalent to the MR formulation, as the ratios for C_{max} and $AUC_{0–inf}$ are both outside the well accepted 0.8–1.25 range needed for bio-equivalence. The terminal elimination half-life values were comparable between all formulations.

Tamsulosin OCAS 0.4 mg S3 came closest to the pre-defined profile of a decreased $C_{max,}$ a low C_{max}/C_{24h} ratio and an acceptable AUC and was selected for further development.

4.3. In vitro/in vivo correlation

Three different OCAS formulations (S2, S3 and S4) containing 0.4 mg tamsulosin hydrochloride were tested in study one against tamsulosin MR 0.4 mg capsules. The rate of *in vitro* dissolution decreased in the order S2, S3, S4 (Fig. 3). An *in vitro/in vivo* correlation was performed to link the AUC_{last}, $AUC_{0–inf}$ and C_{max} values of the single dose PK evaluation with the percentage of the dose dissolved *in vitro* at 3, 7 and 12 h. AUC_{last}, $AUC_{0–inf}$ and C_{max} of

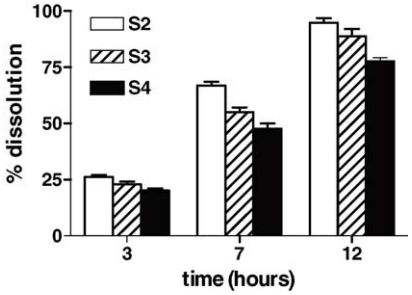

Fig. 3. Tamsulosin OCAS 0.4 mg tablet dissolution data ($n = 6$). Dissolution was carried out for the S2, S3 and S4 formulations using the Ph Eur paddle method (200 rpm) using water at 37 °C as the dissolution medium. Data are expressed as mean ± standard deviation.

the three tamsulosin OCAS formulations increased with increasing rate of *in vitro* dissolution. AUC_{last} and $AUC_{0–inf}$ correlated best with the percentage of the dose dissolved after 12 h ($r^2 = 0.9994$ and 0.9991, respectively), while C_{max} showed the highest correlation with the percentage of the dose dissolved after 7 h ($r^2 = 0.9994$).

4.4. Multiple dose pharmacokinetics

In study two, tamsulosin OCAS formulation S3 was administered once daily for five days to 24 healthy male volunteers. Three doses of tamsulosin OCAS (i.e. 0.4 mg, 0.8 mg, and 1.2 mg) were tested under fasting conditions; one dose (0.4 mg) was also tested under fed conditions.

Fig. 4 shows the mean trough concentration throughout the dosing period. The trough concentration did not increase further from the third day of dosing, demonstrating that the data achieved at dosing

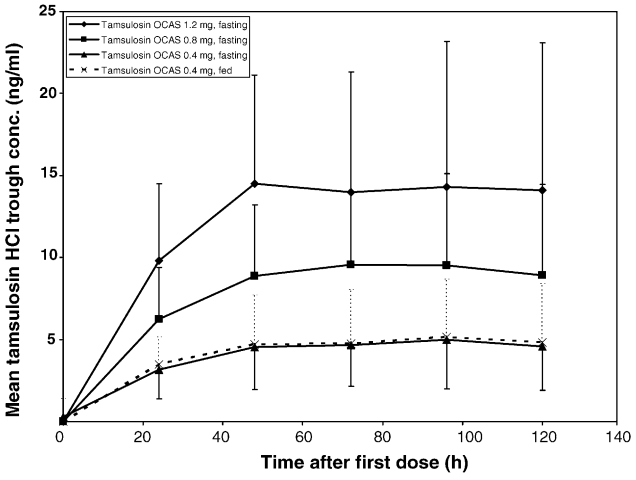

Fig. 4. Mean trough plasma concentrations during multiple dosing of one (0.4 mg), two (0.8 mg) or three (1.2 mg) tablets of tamsulosin OCAS S3 0.4 mg in the fasted state and one tablet of tamsulosin OCAS S3 0.4 mg in the fed state. The curves represent the average values of 24 subjects; the error bars represent the standard deviation.

Table 2
Multiple dose PK parameters of tamsulosin OCAS 0.4, 08 and 1.2 mg S3 formulation in the fasted state and OCAS 0.4 mg S3 formulation in the fed state

Parameter	Tamsulosin OCAS 0.4 mg, fed ($n = 24$)	Tamsulosin OCAS 0.4 mg, fasted ($n = 24$)	Tamsulosin OCAS 0.8 mg, fasted ($n = 24$)	Tamsulosin OCAS 1.2 mg, fasted ($n = 24$)
AUC_{0-24h} (ng·h/ml)	165.9	162.4	321.2	483.6
	(42%)	(64%)	(49%)	(50%)
	68–384	60–422	142–728	178–1088
	149.5	111.7	284.7	435.7
AUC_{0-inf} (ng·h/ml)	291.1	278.7	541.8	850.4
	(68%)	(78%)	(67%)	(69%)
	91–894	89–743	177–1538	240–2528
	223.4	188.1	438.0	602.9
t_{max} (h)	4.16	4.75	4.83	5.26
	(35%)	(35%)	(30%)	(32%)
	2.0–7.0	2.0–7.0	3.0–8.0	2.0–8.0
	4.00	5.00	4.00	5.05
C_{max} (ng/ml)	11.1	10.7	21.3	31.6
	(33%)	(52%)	(41%)	(43%)
	4.7–21.4	5.1–23.2	10.5–41.5	14.5–64.5
	11.2	8.1	19.0	29.5
C_{24h} (ng/ml)	4.8	4.6	8.9	14.1
	(55%)	(78%)	(62%)	(63%)
	1.6–13.7	1.0–12.8	0.7–24.8	2.6–37.9
	4.2	3.4	7.5	10.6
$t_{1/2}$ (h)	14.6	15.6	14.0	14.7
	(48%)	(28%)	(38%)	(39%)
	9.2–43.5	9.3–26.6	6.0–32.4	9.2–33.4
	12.3	14.8	13.2	12.1
TPF	0.421	0.404	0.408	0.424
	(28%)	(36%)	(35%)	(27%)
	0.230–0.639	0.068–0.595	0.045–0.661	0.166–0.764
	0.403	0.440	0.390	0.427

Each cell contains the arithmetic mean, the coefficient of variation between brackets, the range and the median.

Day 5 (as presented in Table 2) can indeed be considered to represent steady state.

The PK parameters at steady state are presented in Table 2. In the fasted state, C_{max} was reached between 4.75 and 5.26 h after dosing (mean values t_{max}). After C_{max} was reached the plasma concentration of tamsulosin declined with a terminal elimination half-life amounting to 14.0–15.6 h. However, between 16 and 24 h the decrease in plasma concentration proceeded at a slightly slower rate, in accordance with the second peak observed in the single dose study. Mean C_{max} values increased from 10.7 ng/ml at a dose of 0.4 mg to 31.6 ng/ml at a dose of 1.2 mg. The variability of the C_{max} value, as judged by its coefficient of variation, appeared to be independent of dose. Under fasted conditions, both C_{max} and AUC_{0-24h} values appeared to increase in proportion to the dose, indicating dose-linearity for both parameters. The C_{max} and AUC ratios and their 90% confidence limits are presented in Table 3.

4.5. Analysis of food effect

Study two included a dosing period of tamsulosin OCAS 0.4 mg after a standard meal. This allows the comparison with the dosing period with OCAS 0.4 mg fasted to assess the presence of a food effect. The data are presented in Table 2 and a graphic presentation is given in Fig. 5.

Feeding did not affect the mean t_{max} (4.16 h in the fed state vs. 4.75 h in the fasted state) and the mean C_{max} (11.1 ng/ml in the fed state vs. 10.7 ng/ml in the

Table 3
Results of the comparison of AUC_{0-24h} and C_{max} values of the 0.8 mg and 1.2 mg tamsulosin OCAS S3 with the corresponding values obtained with 0.4 mg tamsulosin OCAS S3, fasting

Parameter	Comparison	Ratio	90% confidence limits
AUC_{0-24h}	0.8 mg vs. 0.4 mg fasting	2.099	1.876–2.349
	1.2 mg vs. 0.4 mg fasting	3.128	2.796–3.500
C_{max}	0.8 mg vs. 0.4 mg fasting	2.064	1.831–2.327
	1.2 mg vs. 0.4 mg fasting	3.040	2.697–3.428

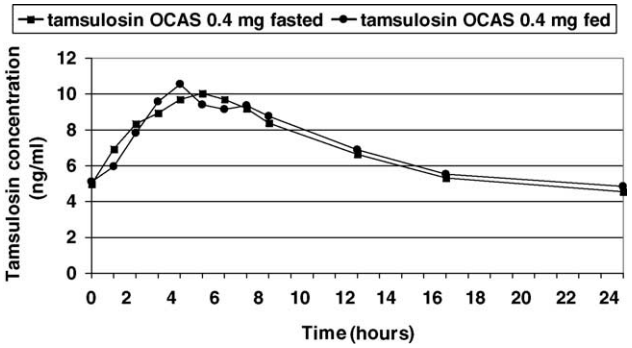

Fig. 5. Mean plasma concentration vs. time profiles of multiple dosing of tamsulosin OCAS S3 0.4 mg in the fasted and the fed state. The curves represent the average values of 24 subjects. A quantitative analysis of the data is presented in Table 2.

fasted state). The mean $t_{1/2}$ was similarly approximately 15 hours in both the fed and fasted state.

In the fed state, the mean C_{24h} was 4.8 ng/ml which is comparable to the value found in the fasted state (4.6 ng/ml). If administered together with food, $AUC_{0–24h}$ values were essentially not affected.

Since for both the C_{max} and the $AUC_{0–24h}$, the 90% confidence interval fell within the limits of 0.80–1.25, the C_{max} and $AUC_{0–24h}$ obtained under fast and fed conditions can be considered equivalent (Table 4). Hence, the PK of the tamsulosin OCAS formulation appear to be unaffected by concomitant food intake.

4.6. Safety/tolerability results

In study one, 15 subjects were exposed to the three tamsulosin OCAS 0.4 mg formulations and the tamsulosin MR 0.4 mg capsules. Three subjects were withdrawn during the first dosing group for either personal reasons (two times) or a dosing error (once). No withdrawals were caused by AEs. No serious AEs were reported in this study and all AEs reported (in nine out of 15 subjects) were of mild intensity. The most commonly occurring event was headache in five subjects followed by dizziness in two subjects.

24 subjects were enrolled in study two. 123 AEs were reported by 18 of the 24 subjects. There were no withdrawals due to AEs and no serious AEs. Only two severe (2 cases of tooth pain, considered to be unrelated) and twenty-two moderate AEs were reported, the other 99 AEs were considered mild. The most common adverse events reported were headache, rash, dizziness, and vomiting. Headache and rash were reported both 16 times (13.0%) by eight and seven subjects, respectively. Dizziness was reported 10 times (8.1%) by six subjects, and vomiting was reported nine times (7.3%) by two subjects.

The total number of adverse events was highest in the tamsulosin OCAS 1.2 mg group. Forty-nine adverse events (39.8%) were reported after receiving tamsulosin OCAS 1.2 mg, In the fasted state, 26 events (21.1%) after receiving 0.8 mg and 24 events (19.5%) after receiving 0.4 mg and 24 events (19.5%) after receiving tamsulosin OCAS 0.4 mg in the fed state.

The clinical laboratory evaluation and the vital signs assessment did not generate evidence of drug-related effects.

Table 4
Results of the statistical test for the presence of a food effect on $AUC_{0–24h}$ and C_{max} with tamsulosin OCAS 0.4 mg

Parameter	Ratio	90% confidence limits	Equivalence
$AUC_{0–24h}$	1.115	0.996–1.248	Yes
C_{max}	1.104	0.979–1.245	Yes

5. Discussion

Tamsulosin 0.4 mg is a well established treatment of LUTS/BPH in its MR capsule formulation which contains coated pellets. This paper describes the PK of a newly developed controlled release formulation: tamsulosin OCAS®. The OCAS® technology is a new proprietary formulation technology which differs from the technologies used for the prolonged release forms of alfuzosin and doxazosin in a way that the OCAS® technology results in a tablet that becomes fully hydrated in the GI tract before reaching the colon and therefore can continue to release tamsulosin while passing through the colon which contains relatively little water. This has the advantage that release of tamsulosin from the new formulation is prolonged in a controlled way for a longer period of time, resulting in a further flattened PK profile.

The three OCAS tablet formulations of 0.4 mg tamsulosin with varying amounts of gel content expectedly showed a lower C_{max} and a slightly lower AUC than the MR capsules. Rather than showing a clear peak, tamsulosin OCAS 0.4 mg showed a more or less steady plasma level between 6 en 24 hours after dosing, resulting in a reduced fluctuation of the plasma concentration over 24 hours with an improved C_{max}/C_{24h} ratio. The elimination half life was not affected by the formulation. Tamsulosin OCAS formulation S3 was selected for further development because it showed the best compromise between an improved C_{max}/C_{24h} ratio and a reasonable bioavailability.

The multiple dose PK of the tamsulosin OCAS formulation S3 was determined with drug doses of 0.4, 0.8 and 1.2 mg. Both C_{max} and AUC appeared to show dose-linearity while there was no effect on the

t_{max} and the $t_{1/2}$ parameters. The changes in PK of the OCAS formulation compared to the MR formulation do not affect the once daily dosing of tamsulosin. Tamsulosin OCAS therefore can be dosed once daily. Comparison of the PK of tamsulosin OCAS 0.4 mg in the fasted state and after a standard meal showed that unlike the MR capsule formulation [12], the OCAS formulation does not exhibit a food effect. This is of clinical relevance as the MR capsule is recommended to be taken after breakfast or the first meal of the day. Lack of compliance of this dosing recommendation with the MR capsule or habituation to taking no breakfast will lead to a larger exposure to tamsulosin than intended, and this can lead to a higher incidence of vasodilatation-related AEs like dizziness, headache, asthenia, tachycardia/palpitation, postural hypotension and syncope [13]. Such a risk will not exist for the OCAS formulation as the PK are not influenced by food. Unfortunately, the multiple dose study did not contain an additional dosing group comprising the tamsulosin MR 0.4 mg capsule. However, since tamsulosin shows linear pharmacokinetics and does not present autoinduction or autoinhibition of metabolising enzymes [23], one may assume that also in steady state a similar difference in plasma concentration - time profiles will occur as observed after a single dose. The C_{max} of OCAS 0.4 mg is therefore expected to remain lower compared with tamsulosin MR 0.4 mg both in the fasted and fed state, while trough levels will not be affected. Since tamsulosin OCAS shows less fluctuation in plasma concentration during a 24-hour time period and its kinetics are not dependent on food intake, this may result in a more favourable safety profile. Furthermore, due to the fact that the pharmacokinetics of tamsulosin OCAS are independent of food intake one may expect that variability in exposure, and consequently in the occurrence of adverse events on the one hand and in the maintenance of adequate 24-hour drug levels on the other hand, within and between subjects will be favourable compared with tamsulosin MR 0.4 mg. Given the reduced fluctuation in plasma concentration profile obtained with tamsulosin OCAS 0.4 mg, a similar efficacy during the day and night is expected.

The AUC of OCAS formulation S3 is only 78% of the AUC of the MR capsules. The selected OCAS formulation is therefore not bio-equivalent to the MR capsules and the actual dose delivered will be smaller for the OCAS formulation than for the MR capsule formulation. Although it can be speculated that maintenance of the plasma tamsulosin above a certain threshold will be more important than the actual dose delivered, this should be determined in clinical studies in LUTS/BPH patients.

6. Conclusions

The tamsulosin OCAS 0.4 mg S3 formulation has been shown to have improved controlled release PK compared with the MR 0.4 mg capsule formulation of tamsulosin. The C_{max} of tamsulosin OCAS is lower and there is less fluctuation in the plasma concentration which is kept at a plateau level for a longer period of time. The new formulation can also be dosed once daily. The lack of a food effect of the OCAS formulation will make exposure to increased levels to tamsulosin due to failure to comply with dosage recommendations less likely to occur which may also result in an improved safety. The actual consequences of these improved controlled release PK as well as the confirmation of the effective dose will have to be done in full scale clinical studies.

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